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Dated 16 January 2004

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Request for grant of a patent

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The Patent Office
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1. Your reference — 4-33154P1/HO 75

2. Patent application number *(The Patent Office will fill in this part)* — 0307856.5 — 04 APR 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

NOVARTIS AG
LICHTSTRASSE 35
4056 BASEL
SWITZERLAND

Patent ADP number *(if you know it)* 7128487 005

If the applicant is a corporate body, give the country/state of its incorporation — SWITZERLAND

4. Title of invention — Organic Compounds

5. Name of your agent *(If you have one)*

[redacted]

B.A. YORKE & CO.
CHARTERED PATENT AGENTS
COOMB HOUSE, 7 ST. JOHN'S ROAD
ISLEWORTH
MIDDLESEX TW7 6NH

1800001

6. If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day/month/year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

(see note (d))

Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	26
Claim(s)	5
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature: B. A. Yorke & Co.

Date: B.A. Yorke & Co. 4 April 2003

12. Name and daytime telephone number of person to contact in the United Kingdom: Mrs. S. Schnerr 020 8560 5847

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Notes

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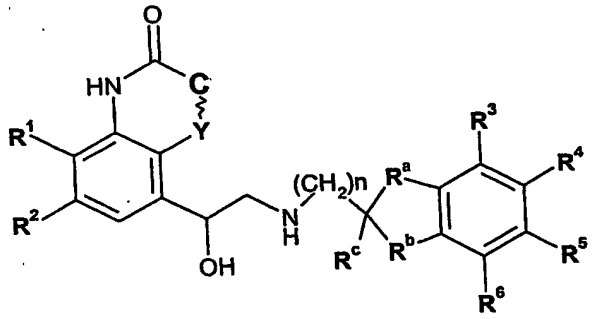
DUPLICATE

ORGANIC COMPOUNDS

This invention relates to organic compounds, their preparation and use as pharmaceuticals.

The invention provides in one aspect a compound of formula I



I

in free or salt or solvate form, where

-C~Y- denotes $-CH_2-CH_2-$, -CH=CH- or $-CH_2-O-$;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is an integer from 0 to 4;

when n is 0, R^a is $-CR^7R^8-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-O-$, $-CH_2-O-CH_2-$, $-CH_2-S-$, $-CH_2-CH_2-S-$, $-CH_2-SO-$, $-CH_2-SO_2-$ or a bond, and R^b is $-CR^9R^{10}-$, $-CH_2-CH_2-CH_2-$, $-CH_2-O-$, $-CH_2-O-CH_2-$, $-CH_2-S-$, $-CH_2-CH_2-S-$, $-CH_2-SO-$, $-CH_2-SO_2-$ or a bond,

otherwise when n is 1, 2, 3 or 4, R^a and R^b are independently $-CR^7R^8-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, -O-, $-CH_2-O-$, $-CH_2-O-CH_2-$, -S-, -SO-, $-SO_2-$, $-CH_2-S-$, $-CH_2-CH_2-S-$, $-CH_2-SO-$, $-CH_2-SO_2-$ or a bond;

R^c is hydrogen or C_1-C_{10}-alkyl optionally substituted by a C_5-C_{15}-carbocyclic group or by C_1-C_{10}-alkoxy,

or when R^b is $-CR^7R^8-$ or $-CR^9R^{10}-$, R^c and R^b form a C_5-C_{15}-carbocyclic group;

R^3, R^4, R^5 and R^6 are independently hydrogen, halo, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, or a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, or any two of R^3, R^4, R^5 and R^6 that are attached to adjacent carbon atoms on the phenylene ring together form a phenylene ring, C_3-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkenyl or 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur;

R^7, R^8 and R^9 are independently hydrogen, C_1-C_{10}-alkyl or C_1-C_{10}-alkoxy, either of which being optionally substituted by a C_5-C_{15}-carbocyclic group; and

R^{10} is C_1-C_{10}-alkyl or C_1-C_{10}-alkoxy, either of which being optionally substituted by a C_5-C_{15}-carbocyclic group.

Terms used in this specification have the following meanings:

"Optionally substituted" as used herein means the group referred to can be substituted at one or more positions by any one or any combination of the radicals listed thereafter.

"C_1-C_{10}-alkyl" as used herein denotes straight chain or branched alkyl, which may be, for example, C_1 to C_{10} alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, straight or branched pentyl, straight or branched hexyl, straight or branched heptyl, straight or branched nonyl or straight or branched decyl. Preferably C_1-C_{10}-alkyl is C_1-C_4-alkyl.

"C_1-C_{10}-alkoxy" as used herein denotes straight chain or branched alkoxy and may be, for example, C_1 to C_{10} alkoxy such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, or straight or branched pentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy or decyloxy. Preferably C_1-C_{10}-alkoxy is C_1-C_4-alkoxy.

"C_3-C_{10}-cycloalkyl" as used herein denotes cycloalkyl having 3 to 10 ring carbon atoms, for example a monocyclic group such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl, any of which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups, or a bicyclic group such as bicycloheptyl or bicyclooctyl. Preferably C_3-C_{10}-cycloalkyl is C_3-C_6-cycloalkyl, for example cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

"C_3-C_{10}-cycloalkenyl" as used herein denotes a hydrocarbon ring that contains 3 to 10 ring carbon atoms and one or more carbon-carbon double bonds, for example a monocyclic group such as a cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl or cyclodecenyl, any of which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups, or a bicyclic group such as bicycloheptenyl or bicyclooctenyl. Preferably C_3-C_{10}-cycloalkenyl is C_3-C_6-cycloalkenyl, for example cyclopropenyl, cyclobutenyl, cyclopentenyl or cyclohexenyl.

"C_5-C_{15}-carbocyclic group" as used herein denotes a carbocyclic group having 5 to 15 ring carbon atoms, for example a monocyclic group, either aromatic or non-aromatic, such as a cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or phenyl, any of which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups, or a bicyclic group such as bicyclooctyl, bicyclononyl, bicyclodecyl, indanyl or indenyl, again any of which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups . Preferably the C_5-C_{15}-carbocyclic group is a C_5-C_{10}-carbocyclic group, for example indanyl.

"Halo" or "halogen" as used herein denotes a element belonging to group 17 (formerly group VII) of the Periodic Table of Elements, which may be, for example, fluorine, chlorine, bromine or iodine. Preferably halo or halogen is bromine.

"5- or 6- membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur" as used herein may be, for example, pyrrole, pyrrolidine, pyrazole, imidazole, triazole, tetrazole, thiadiazole, isothiazole, thiophene, oxadiazole, pyridine, oxazole, isoxazole, pyrazine, pyridazine, pyrimidine, piperazine, morpholino, triazine, oxazine or thiazole. Preferred 5- or 6- membered heterocyclic rings include thiophene, imidazole, thiazole and pyridine. The 5- or 6-membered heterocyclic ring can be unsubstituted or substituted. Preferred substituents on the heterocyclic ring include halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy and C_3-C_{10}-cycloalkyl. Especially preferred substituents on the ring include C_1-C_{10}-alkyl and C_1-C_{10}-alkoxy.

When any two of R^3, R^4, R^5 and R^6 that are attached to adjacent carbon atoms on the phenylene ring together form a phenylene ring, that ring so formed can be unsubstituted or substituted. Preferred substituents on that ring include halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy and C_3-C_{10}-cycloalkyl. Especially preferred substituents on the ring include C_1-C_{10}-alkyl and C_1-C_{10}-alkoxy.

Throughout this specification and in the claims that follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Preferred compounds of the present invention are compounds of formula I where

-C~Y- is -CH=CH-;

R^1 is hydroxy and R^2 is hydrogen;

n is 0 or 1;

when n is 0, R^a is $-CR^7R^8-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-O-CH_2-$ or $-CH_2-CH_2-S-$,

and R^b is $-CR^9R^{10}-$, $-CH_2-O-$ or a bond,

otherwise when n is 1, R^a and R^b are both $-CR^7R^8-$;

R^c is hydrogen or C_1-C_{10}-alkyl optionally substituted by a C_5-C_{15}-carbocyclic group or by C_1-C_{10}-alkoxy,

or when R^b is $-CR^7R^8-$ or $-CR^9R^{10}-$, R^c and R^b form a C_5-C_{15}-carbocyclic group;

R^3, R^4, R^5 and R^6 are independently hydrogen, C_1-C_{10}-alkyl or C_1-C_{10}-alkoxy;

R^7 , R^8 and R^9 are independently hydrogen, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur; and

R^{10} is C_1-C_{10}-alkyl or C_1-C_{10}-alkoxy.

Especially preferred compounds of the present invention are compounds of formula I where

-C~Y- is -CH=CH-;

R^1 is hydroxy and R^2 is hydrogen;

n is 0 or 1;

when n is 0, R^a is $-CR^7R^8-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-O-CH_2-$ or $-CH_2-CH_2-S-$,

and R^b is $-CR^9R^{10}-$, $-CH_2-O-$ or a bond,

otherwise when n is 1, R^a and R^b are both $-CR^7R^8-$;

R^c is hydrogen or C_1-C_4-alkyl optionally substituted by a C_5-C_{10}-carbocyclic group or by C_1-C_4-alkoxy,

or when R^b is $-CR^7R^8-$ or $-CR^9R^{10}-$, R^c and R^b form a C_5-C_{10}-carbocyclic group;

R^3, R^4, R^5 and R^6 are independently hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy;

R^7 , R^8 and R^9 are independently hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy or a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur; and

R^{10} is C_1-C_4-alkyl or C_1-C_4-alkoxy.

The compounds of formula (I) are capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts. Pharmaceutically acceptable acid addition salts of the compound of formula I include those of inorganic acids, for example, hydrohalic

acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid or hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid; and organic acids such as formic acid, acetic acid, propionic acid, butyric acid, benzoic acid, o-hydroxybenzoic acid, p-hydroxybenzoic acid, p-chlorobenzoic acid, diphenylacetic acid, triphenylacetic acid, 1-hydroxynaphthalene-2-carboxylic acid, 3-hydroxynaphthalene-2-carboxylic acid, aliphatic hydroxy acids such as lactic acid, citric acid, tartaric acid or malic acid, dicarboxylic acids such as fumaric acid, maleic acid or succinic acid, and sulfonic acids such as methanesulfonic acid or benzenesulfonic acid. These salts may be prepared from compounds of formula I by known salt-forming procedures.

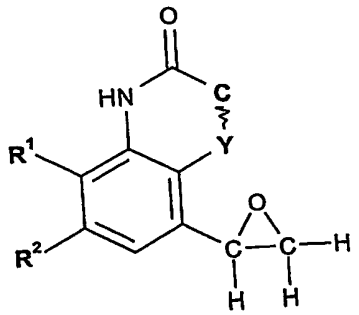
Compounds of formula I which contain acidic, e.g. carboxyl groups, are also capable of forming salts with bases, in particular pharmaceutically acceptable bases such as those well known in the art; suitable such salts include metal salts, particularly alkali metal or alkaline earth metal salts such as sodium, potassium, magnesium or calcium salts, or salts with ammonia or pharmaceutically acceptable organic amines or heterocyclic bases such as ethanolamines, benzylamines or pyridine. These salts may be prepared from compounds of formula I by known salt-forming procedures.

In those compounds where there is an asymmetric carbon atom the compounds exist in individual optically active isomeric forms or as mixtures thereof, e.g. as racemic or diastereomeric mixtures. The present invention embraces individual optically active R and S isomers as well as mixtures, e.g. racemic or diastereomeric mixtures, thereof.

Specific especially preferred compounds of the invention are those described hereinafter in the Examples.

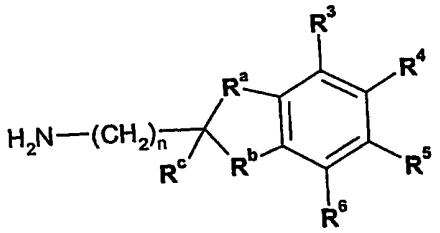
The present invention also provides a process for the preparation of compounds of formula I in free or salt or solvate form. They can be prepared by a process comprising:

(i) (A) reacting a compound of formula II



II

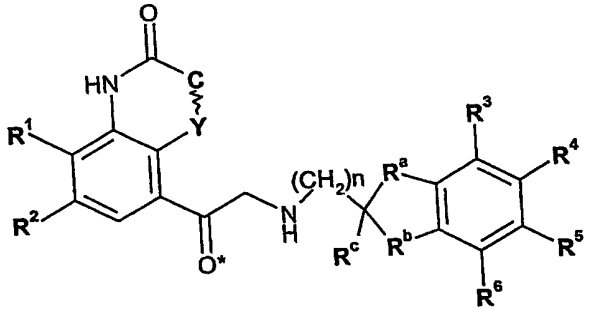
or a protected form thereof wherein -C-Y-, R^1 and R^2 are as hereinbefore defined, with a compound of formula III



III

or a protected form thereof wherein R^a, R^b, R^c, R^3, R^4, R^5, R^6 and n are as hereinbefore defined;

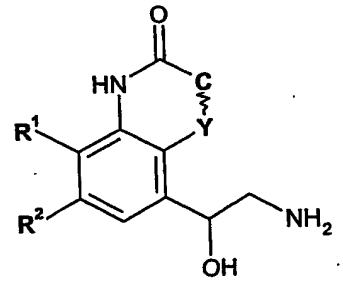
(B) reducing a compound of formula IV



IV

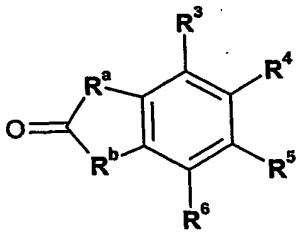
or a protected form thereof wherein -C~Y-, R^a, R^b, R^c, R^1, R^2, R^3, R^4, R^5, R^6 and n are as hereinbefore defined, to convert the indicated keto group into -CH(OH); or

(C) for the preparation of compounds of formula I where R^c is hydrogen and n is 0, reacting a compound of formula V



V

or a protected form thereof wherein -C~Y-, R^1 and R^2 are as hereinbefore defined, with a compound of formula VI



VI

or a protected form thereof wherein R^a, R^b, R^3, R^4, R^5 and R^6 are as hereinbefore defined; and

(ii) recovering the resultant compound of formula I in free or salt or solvate form.

Process variant (A) may be carried out using known procedures for reacting epoxides with amines or analogously as hereinafter described in the Examples. The reaction is conveniently carried out without a solvent or in an inert solvent, for example an organic solvent such as 2-methoxyethyl ether or N,N'-dimethylformamide in the presence of a silylating agent such as N,O-bis(trimethylsilyl)acetamide. The reaction temperature is conveniently from 25°C to 200°C, preferably from 80°C to 190°C. The temperature may be achieved by conventional heating or by microwave irradiation.

Process variant (B) may be carried out using conventional methods, for example by hydrogenation using a suitable catalyst such as Pd/C or by reaction with sodium borohydride or a borane reducing agent under conventional conditions.

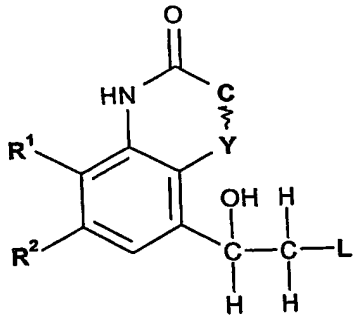
Process variant (C) may be carried out using known procedures for reacting amino alcohols with ketones or analogously under reductive animation conditions as hereinafter described in the Examples. The reaction is conveniently carried out using a borohydride salt under acidic conditions, for example sodium triacetoxyborohydride and acetic acid, and using an organic solvent, for example 1,2-dichloromethane, as described in J. Org. Chem. 1996, 61,

3849. The reaction temperature is conveniently from 0° C to 25° C, preferably room temperature.

Compounds of formula I in free form may be converted into salt form, and vice versa, in a conventional manner. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallisation. Compounds of formula I can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as enantiomers, may be obtained in a conventional manner, e.g. by fractional crystallisation or asymmetric synthesis from correspondingly asymmetrically substituted, e.g. optically active, starting materials.

Compounds of formula II are known compounds or can be prepared by processes analogous to those used for the preparation of the known compounds, for example the procedures described in J. Med. Chem. 1987, 30, 1563.

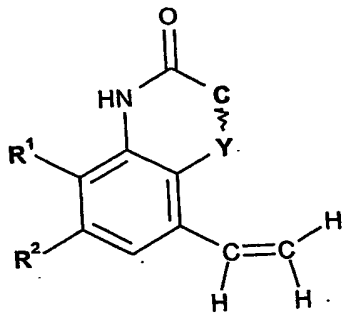
Compounds of formula II in which the carbon atom of the epoxide ring that is attached to the phenyl group is chiral may be prepared from a compound of formula VII



VII

or a protected form thereof where -C~Y-, R^1 and R^2 are as hereinbefore defined and L is a leaving atom or group, as described in international patent application WO 95/25104 or analogously as hereinafter described in the Examples.

Compounds of formula II may alternatively be prepared by epoxidation of a compound of formula VIII

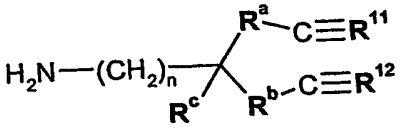


VIII

or a protected form thereof -C~Y-, R^1 and R^2 are as hereinbefore defined, using conventional procedures.

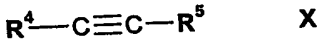
Compounds of formula III are known or may be prepared by methods analogous to those used for the preparation of the known compounds. The amine group may be protected by known methods, for example using an amine-protective group described in Protective Groups in Organic Synthesis, T. W. Greene, P.G.M. Wuts, John Wiley & Sons Inc, Third Edition, 1999, preferably benzyl or trifluoroacetyl.

Compounds of formula III where R^3 and R^6 are hydrogen can be prepared by reacting a compound of formula IX



IX

where R^a, R^b, R^c and n are as hereinbefore defined and R^{11} and R^{12} are each independently hydrogen or C_1-C_{10}-alkyl, with a compound of formula X

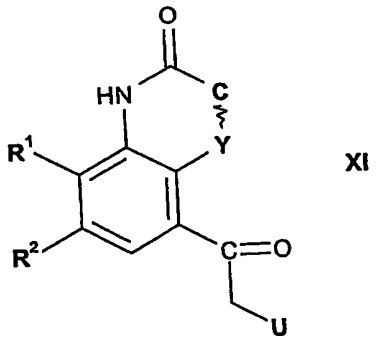


X

where R^4 and R^5 are as hereinbefore defined. The reaction may be carried out using known procedures, for example as described in international patent application WO 96/23760 or analogously as hereinafter described in the Examples. The reaction is conveniently carried out in an inert solvent, for example ethanol, preferably in the presence of a catalyst such as tris(triphenylphosphine)rhodium chloride. The reaction temperature is conveniently from 60 to 120°C , preferably from 80 to 100°C. Where R^4 and R^5 are trialkylsilyl, the reaction between the compounds of formulae IX and X may be carried out in the presence of a metal carbonyl complex catalyst, for example using the procedure described by K.P.C. Vollhardt and R. Hillard, J. Am. Chem. Soc. 1977, 99, 4058.

Compounds of formula III where R^c is C_1-C_{10}-alkyl optionally substituted by a C_5-C_{15}-carbocyclic group or by C_1-C_{10}-alkoxy, and R^b and R^c are both methylene may be prepared by amination of the corresponding 2-alkyl-indan-1-one using ammonia and $K_3Fe(CN)_6$, for example using the procedure described in Fornum and Carlson, Synthesis 1972, 191, or analogously as hereinafter described in the Examples.

Compounds of formula IV are novel compounds which may be prepared by reaction of a compound of formula XI



XI

or a protected form thereof where -C~Y-, R^1 and R^2 are as hereinbefore defined and U is a halogen atom, preferably chlorine or bromine, with a compound of formula III as hereinbefore defined. The reaction may be carried out using conventional procedures, for example those described by Yoshizaki et al, J. Med. Chem 1976, 19, 1138, or analogously as hereinafter described in the Examples.

Compounds of formula V are known or may be prepared by reacting a compound of formula II where Y, R^1 and R^2 are as hereinbefore defined with ammonia or a protected form thereof or azide using known methods for reacting epoxides with amines or analogously as hereinafter described in the Examples. Where a compound of formula II is reacted with azide a reduction step is subsequently required to yield the compound of formula V.

Compounds of formula VI are known or may be prepared by known procedures such as those described in Liebigs Ann. Chem. 1985, 435.

Compounds of formula VII are known or may be prepared by methods analogous to those used for the preparation of known compounds, for example those used in the Examples hereinafter.

Compounds of formula VIII are known or may be prepared by known procedures.

Compounds of formula IX may be prepared as described in international patent application WO 96/23760 or by analogous procedures.

Compounds of formula X are known or may be prepared by known procedures.

Compounds of formula XI are known or may be prepared by known procedures, for example those disclosed in United States patent specification US 4460581 and German patent specification DE 3134590.

Where desired, the protection of any reactive group may be carried out at any appropriate stage in the above processes. The protecting group is suitably one used conventionally in the art and may be introduced and removed using conventional procedure. For example, when a hydroxy group is protected by a benzyl group, the latter may be removed by catalytic hydrogenation in the presence of palladium on charcoal using conventional procedures, such as those used hereinafter in the Examples.

Compounds of formula I in free, salt or solvate form are useful as pharmaceuticals. Accordingly the invention also provides a compound of formula I in free, salt or solvate form for use as a pharmaceutical. The compounds of formula I in free, salt or solvate form, hereinafter referred to alternatively as "agents of the invention", have good β_2-adreno-receptor agonist activity. The β_2 agonist activity, onset of action and duration of action of the agents of the invention may be tested using the guinea pig tracheal strip in vitro assay according to the procedure of R.A. Coleman and A.T. Nials, J. Pharmacol. Methods 1989, 21, 71. The binding potency and selectivity for the β2-adrenoreceptor relative to the β1-adrenoreceptor can be measured by a classical filtration binding assay according to the procedure of Current Protocols in Pharmacology (S. J. Enna (editor-in-chief) et al, John Wiley & Son, Inc, 1998), or by cAMP determination in cells expressing β2- or β1-adrenoceptor, according to the procedure of B. January et al, Brit. J. Pharmacol. 1998, 123, 701.

The agents of the invention commonly have a rapid onset of action and have a prolonged stimulating action on the β_2-adrenoreceptor, compounds of the Examples hereinbelow

having K_i (β_2) values of the order of 0.1 to 1000 nM, having durations of action of the order of 1 to greater than 12 hours. Many of the compounds have binding selectivities for the β_2-adrenoreceptor relative to the β_1-adrenoreceptor from 1.5 to 500. The compounds of Examples 1, 3 and 4 have β_2 and β_1 binding potencies, measured by a classical filtration binding assay, represented by K_i values (β_2/β_1) (in μM) of 0.026/0.186, 0.054/0.050 and 0.006/0.115 respectively.

Having regard to their β_2 agonist activity, the agents of the invention are suitable for use in the treatment of any condition which is prevented or alleviated by activation of the β_2-adrenoreceptor. In view of their long acting selective β_2 agonist activity, the agents of the invention are useful in the relaxation of bronchial smooth muscle and the relief of bronchoconstriction. Relief of bronchoconstriction can be measured in models such as the in vivo plethysmography models of Chong et al, J. Pharmacol. Toxicol. Methods 1998, 39, 163, Hammelmann et al, Am. J. Respir. Crit. Care Med., 1997, 156, 766 and analogous models. The agents of the invention are therefore useful in the treatment of obstructive or inflammatory airways diseases. In view of their long duration of action, it is possible to administer the agents of the invention once-a-day in the treatment of such diseases. In another aspect, agents of the invention commonly exhibit characteristics indicating a low incidence of side effects commonly encountered with β_2 agonists such as tachycardia, tremor and restlessness, such agents accordingly being suitable for use in on demand (rescue) treatment as well as prophylactic treatment of obstructive or inflammatory airways diseases.

Treatment of a disease in accordance with the invention may be symptomatic or prophylactic treatment. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be

evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant from any previously administered symptomatic asthma therapy.

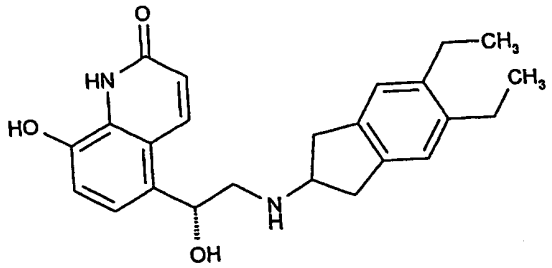
Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary or airways disease (COPD or COAD), including chronic bronchitis, or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Having regard to their β_2 agonist activity, the agents of the invention are also useful in the treatment of a condition requiring relaxation of smooth muscle of the uterus or vascular system. They are thus useful for the prevention or alleviation of premature labour pains in pregnancy. They are also useful in the treatment of chronic and acute urticaria, psoriasis, allergic conjunctivitis, actinitis, hay fever, and mastocytosis.

The agents of the invention are also useful as co-therapeutic agents for use in combination with other drug substances such as anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. An agent of the invention may be mixed with the other drug

substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance. Accordingly the invention includes a combination of an agent of the invention as hereinbefore described with an anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substance, said agent of the invention and said drug substance being in the same or different pharmaceutical composition. Such anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone dipropionate, fluticasone propionate, ciclesonide or mometasone furoate and compounds described in WO 0200679, WO 0288167, WO 0212266 and WO 02100879, LTB4 antagonists such as those described in US 5451700, LTB4 antagonists such as those described in US 5451700, LTD4 antagonists such as montelukast and zafirlukast, PDE4 inhibitors such as Ariflo® (GlaxoSmith Kline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene) and KW-4490 (Kyowa Hakko Kogyo) and A2a agonists such as those described in EP 1052264, EP 1241176, WO 0023457, WO0077018, WO 0123399, WO 0160835, WO 0194368, WO 0200676, WO 0222630, WO 0296462, WO 0127130, WO 0127131, WO 9602543, WO 9602553, WO 9828319, WO 9924449, WO 9924450, WO 9924451, WO 9938877, WO 9941267, WO 9967263, WO 9967264, WO 9967265, WO 9967266, WO 9417090, EP 409595A2 and WO 0078774 and A2b antagonists such as those described in WO 0242298. Such bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular ipratropium bromide, oxitropium bromide and tiotropium bromide.

The agents of the invention are also useful as co-therapeutic agents for use in combination other beta-2 adrenoceptor agonists, for example as a rescue medication. Suitable beta-2 adrenoceptor agonists include salbutamol, terbutaline, salmeterol and, especially, formoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula I of PCT International patent publication No. WO 0075114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



and pharmaceutically acceptable salts thereof.

Co-therapeutic antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride.

Combinations of agents of the invention and steroids, PDE4 inhibitors, A2a agonists, A2b agonists or LTD4 antagonists may be used, for example, in the treatment of COPD or, particularly, asthma. Combinations of agents of the invention and anticholinergic or antimuscarinic agents, PDE4 inhibitors, A2a agonists, A2b agonists, dopamine receptor agonists or LTB4 antagonists may be used, for example, in the treatment of asthma or, particularly, COPD.

In accordance with the foregoing, the present invention also provides a method for the treatment of an obstructive or inflammatory airways disease which comprises administering to a subject, particularly a human subject, in need thereof a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore described. In another aspect, the invention provides a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore described for use in the preparation of a medicament for the treatment of an obstructive or inflammatory airways disease.

The agents of the invention may be administered by any appropriate route, e.g. orally, for example in the form of a tablet or capsule; parenterally, for example intravenously; topically to the skin, for example in the treatment of psoriasis; intranasally, for example in the treatment of hay fever; or, preferably, by inhalation, particularly in the treatment of obstructive or inflammatory airways diseases.

In a further aspect, the invention also provides a pharmaceutical composition comprising a compound of formula I in free form or in the form of a pharmaceutically acceptable salt or solvate thereof, optionally together with a pharmaceutically acceptable diluent or carrier therefor. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g. patches. Compositions for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

When the composition comprises an aerosol formulation, it preferably contains, for example, a hydro-fluoro-alkane (HFA) propellant such as HFA134a or HFA227 or a mixture of these, and may contain one or more co-solvents known in the art such as ethanol (up to 20% by weight), and/or one or more surfactants such as oleic acid or sorbitan trioleate, and/or one or more bulking agents such as lactose. When the composition comprises a dry powder formulation, it preferably contains, for example, the compound of formula I having a particle diameter up to 10 microns, optionally together with a diluent or carrier, such as lactose, of the desired particle size distribution and a compound that helps to protect against product performance deterioration due to moisture. When the composition comprises a nebulised formulation, it preferably contains, for example, the compound of formula I either dissolved, or suspended, in a vehicle containing water, a co-solvent such as ethanol or propylene glycol and a stabiliser, which may be a surfactant.

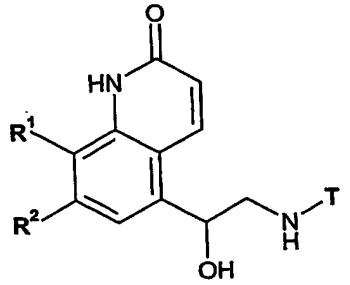
The invention also includes (A) a compound of formula I as hereinbefore described in free form, or a pharmaceutically acceptable salt or solvate thereof, in inhalable form; (B) an inhalable medicament comprising such a compound in inhalable form together with a pharmaceutically acceptable carrier in inhalable form; (C) a pharmaceutical product comprising such a compound in inhalable form in association with an inhalation device; and (D) an inhalation device containing such a compound in inhalable form.

Dosages employed in practising the invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of from 1 to 5000 μg.

The invention is illustrated by the following Examples.

Examples

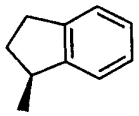
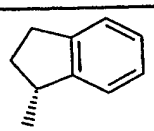
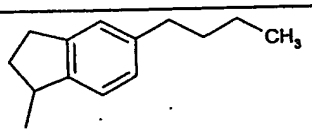
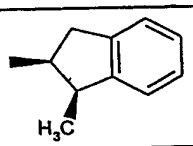
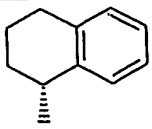
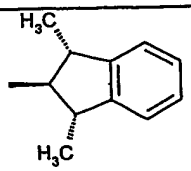
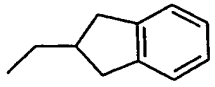
Especially preferred compounds of formula I are also compounds of formula XII

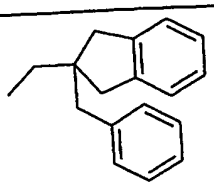
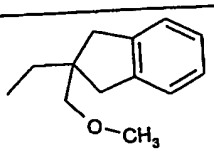
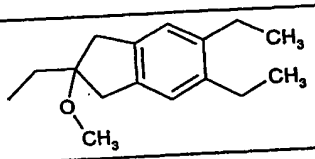
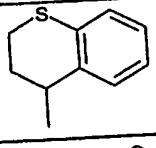
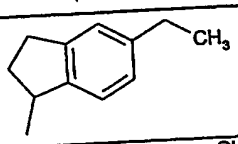
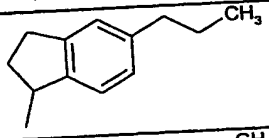
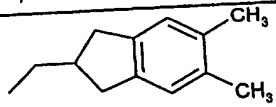
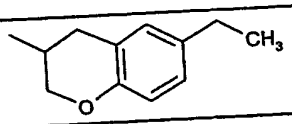
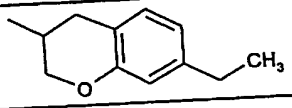
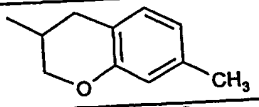
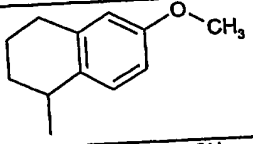
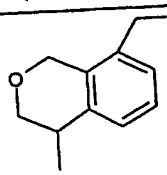


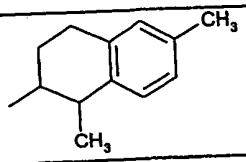
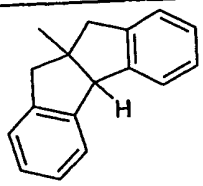
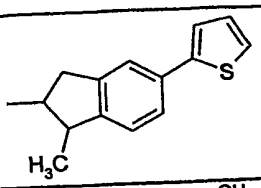
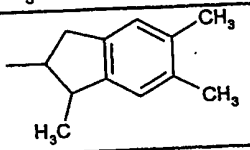
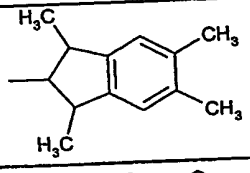
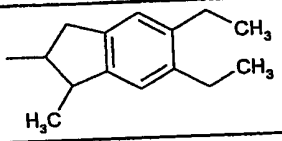
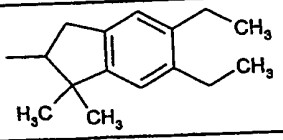
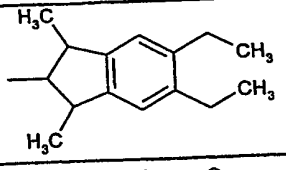
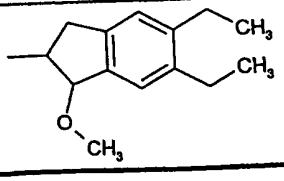
XII

wherein T is as shown in the following table, the method of preparation being described hereinafter. All compounds are in the free form. 1H NMR spectra are recorded at 400 MHz in $CDCl_3$ unless otherwise noted. Mass spectra are obtained under electrospray ionisation conditions with LC gradient elution of 5% to 95% acetonitrile-water in the presence of 0.1% formic acid.

TABLE I

Ex	R^1	R^2	T	MH^+
1	-OH	-H		337
2	-OH	-H		337
3	-OH	-H		393
4	-OH	-H		351
5	-OH	-H		351
6	-OH	-H		362
7	-OH	-H		351

8	-OH	-H		-
9	-OH	-H		-
10	-OH	-H		-
11	-OH	-H		
12	-OH	-H		-
13	-OH	-H		-
14	-OH	-H		-
15	-OH	-H		-
16	-OH	-H		-
17	-OH	-H		-
18	-OH	-H		-
19	-OH	-H		-

20	-OH	-H		-
21	-OH	-H		
22	-OH	-H		
23	-OH	-H		-
24	-OH	-H		-
25	-OH	-H		-
26	-OH	-H		-
27	-OH	-H		-
28	-OH	-H		-

Preparation of starting materials

2,2',4-Trimethoxybenzophenone oxime

Hydroxylamine hydrochloride (4.98 g, 71.7 mmol) is added to a solution of 2,2',4-trimethoxybenzophenone (J. Org. Chem. 1996, 61, 6326; 6.5 g, 23.9 mmol) in ethanol (50 ml) and pyridine (10 ml). The mixture is heated at reflux for 2 hours and the solvent evaporated. The residue is partitioned between dichloromethane and 2 M aqueous HCl and the organic phase is washed with water, brine, dried ($MgSO_4$) and evaporated to afford the title compound.

C-(2,4-Dimethoxyphenyl)-C-(2-methoxyphenyl)methylamine

2,2',4-Trimethoxybenzophenone oxime (6 g, 20.9 mmol) is dissolved in ethanol (30 ml) and concentrated aqueous ammonia (150 ml). Ammonium acetate (0.81 g, 10.45 mmol) is added, followed by zinc powder (6.79 g, 104 mmol). The reaction is heated to reflux for 4 hours, cooled to ambient temperature, diluted with ethyl acetate and filtered through a Celite™ filter. Evaporation affords the title compound. δ_H 3.78 (s 3H), 3.80 (s 3H), 3.82 (s 3H), 5.62 (s 3H), 6.40-6.50 (m 2H), 6.85-9.95 (m 2H), 7.10 (d *J* 8), 7.20-7.30 (m 2H).

8-Benzyloxy-5-(*R*-2-{[(2,4-dimethoxyphenyl)-(2-methoxyphenyl)methyl]amino}-1-hydroxyethyl)-1H-quinolin-2-one

A mixture of C-(2,4-dimethoxyphenyl)-C-(2-methoxyphenyl)methylamine (0.934 g, 3.42 mmol) and *R*-8-benzyloxy-5-oxiranyl-1H-quinolin-2-one (0.50 g, 1.71 mmol) in $CHCl_3$ (2 ml) is heated at 110°C and the solvent allowed to evaporate. The residue is heated for 16 hours to afford the title compound, *MH*+ 567.

5-(*R*-2-Amino-1-hydroxyethyl)-8-benzyloxy-1H-quinolin-2-one

A solution of 8-benzyloxy-5-(*R*-2-{[(2,4-dimethoxyphenyl)-(2-methoxyphenyl)methyl]-amino}-1-hydroxyethyl)-1H-quinolin-2-one (0.70 g, 1.24 mmol) in acetic acid (10 ml) and water (10 ml) is heated at 80°C for 4 hours. The solvent is evaporated and the crude product purified by reverse phase flash chromatography, eluting with 0% to 50% acetonitrile-water gradient to afford the title compound. δ_H 2.65 (m 1H), 2.95 (m 1H), 3.70-3.80 (m 11H), 5.10 (m 1H), 5.15 (s 1H), 5.55 (m 1H), 6.40-7.40 (m 16H), 7.9 (m 1H), 9.10 (br s 1H).

1-(4-*n*-Butylphenyl)-3-chloropropan-1-one

A mixture of 3-chloropropionyl chloride (8.59 ml, 89.9 mmol) and *n*-butylbenzene (14.02 ml, 89.9 mol) is added dropwise to a cooled (0°C) solution of aluminium chloride (26.93 g, 202 mmol) in nitromethane (54 ml). The mixture is allowed to warm to ambient temperature for 4 hrs, then poured into a mixture of ice and concentrated hydrochloric

acid. The layers are separated and the aqueous phase is extracted with ether. The combined organic phases are washed with brine, dried ($MgSO_4$) and evaporated to afford the title compound, NMR δ_H 0.85 (t *J* 7.3 3H), 1.25 (sextet *J* 7.3 2H), 1.55 (quintet *J* 7.3 2H), 3.34 (t *J* 6.9 2H), 3.84 (t *J* 6.9 2H), 7.20 (d *J* 8.3 2H), 7.80 (d *J* 8.3 2H).

5-*n*-Butylindan-1-one

A solution of 1-(4-*n*-butylphenyl)-3-chloropropan-1-one (17.88 g, 79.8 mmol) in concentrated sulphuric acid (69 ml) is heated at 90°C for 4 hours. After cooling to ambient temperature, the reaction mixture is poured on to ice and extracted with toluene. The combined organic phases are washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$) and evaporated to afford the title compound. NMR δ_H 0.85 (t *J* 7.3 3H), 1.28 (sextet *J* 7.3 2H), 1.56 (quintet *J* 7.3 2H), 2.6 (m 4H), 3.02 (t *J* 5 2H), 7.10 (d *J* 8.3 1H), 7.20 (s 1H), 7.60 (d *J* 8.3 2H).

5-*n*-Butylindan-1-one oxime

Hydroxylamine hydrochloride (0.89 g, 12.8 mmol) and sodium acetate (12.8 mmol) are added to a solution of 5-*n*-butylindan-1-one (1.0 g, 5.31 mmol) in ethanol (30 ml) and water (3 ml). The reaction is heated to reflux for 20 minutes, then water is added and the mixture is extracted with CH_2Cl_2. The combined organic extracts are washed with brine, dried ($MgSO_4$) and evaporated to afford the title compound. NMR δ_H 0.86 (t *J* 7.3 3H), 1.28 (sextet *J* 7.3 2H), 1.52 (quintet *J* 7.3 2H), 2.55 (t *J* 8.0 2H), 2.85-3.0 (m 4H), 7.0 (d *J* 8.3 1H), 7.05 (s 1H), 7.45 (d *J* 8.3 2H).

5-*n*-Butylindan-1-ylamine

A suspension of 5-*n*-butylindan-1-one oxime (0.50 g, 2.46 mmol) and 10% Pd/C (0.50 g) in acetic acid (50 ml) is hydrogenated at 3.5 bar for 16 hours. The reaction is filtered through a Celite™ filter pad and partitioned between ether and water. The organic phase is washed with saturated $NaHCO_3$ then brine and dried ($MgSO_4$). Evaporation affords the title compound. NMR δ_H 0.85 (t *J* 7.3 3H), 1.26 (sextet *J* 7.3 2H), 1.50 (quintet *J* 7.3 2H), 1.58 (m 1H), 2.10 (br s 1H), 2.40 (m 1H), 2.50 (t *J* 8.0 2H), 2.70 (m 1H), 2.88 (m 1H), 4.38 (t *J* 6 1H), 6.95 (m 3H), 7.16 (d *J* 8.3 2H).

Methyl 3-phenylbutyrate

Thionyl chloride (44 ml, 91.4 mmol) is added dropwise to methanol (30 ml) at 0°C, followed by 3-phenylbutyric acid (10 g, 60.9 mmol). The reaction is stirred for 4 hours and the solvent is evaporated. The residue is partitioned between *t*-butylmethyl ether and

aqueous ammonia. The organic phase is washed with water and brine, dried (Na_2SO_4) and evaporated to afford the title compound. *MH*+ 179.

Methyl 2-acetyl-3-phenylbutyrate

n-Butyllithium (2.5 M hexanes 12.4 ml, 30.9 mmol) is added to *N,N*-diisopropylamine (4.4 ml, 31.4 mmol) in tetrahydrofuran (THF, 50 ml) at 0°C. After 10 minutes, the resultant solution is transferred *via* cannula to a cooled (-78°C) solution of methyl 3-phenylbutyrate (5.0 g, 28.05 mmol) in THF (50 ml). After 40 minutes, the resultant solution is transferred *via* cannula to a solution of acetyl chloride (19.15 ml) in THF (50 ml). The resultant mixture is stirred at -78°C for 1.5 hours, then warmed to 0°C after which water is added and the mixture is then poured into saturated $NaHCO_3$ and extracted with EtOAc. The combined organic phases are washed with brine, dried ($MgSO_4$) and evaporated. Purification by flash chromatography (12:1 EtOAc-hexane elution) affords the title compound. δ_H 1.3 (d *J* 7 3H), 2.3 (s 3H), 3.4 (s 3H), 3.6 (m 1H), 3.8 (m 1H), 7.2-7.4 (m 5H).

1,3-Dimethyl-*1H*-indene-2-carboxylic acid

Concentrated sulphuric acid (15 ml) is added to methyl 2-acetyl-3-phenylbutyrate (2.75 g, 12.5 mmol) maintaining the temperature below 30°C. The reaction is stirred at ambient temperature for 5 hours, poured on to ice and extracted with EtOAc. The combined organic extracts are evaporated and the residue is diluted with water and the pH adjusted to 8 with saturated $NaHCO_3$. After washing with EtOAc, the aqueous phase is acidified with concentrated HCl and extracted with EtOAc. The combined organic phases are washed with brine, dried ($MgSO_4$) and evaporated to afford the title compound, *MH*+ 189.

(*1S,2S,3R*)-1,3-Dimethylindan-2-carboxylic acid

A suspension of 1,3-dimethyl-*1H*-indene-2-carboxylic acid (0.362 g, 1.92 mmol) and 10% palladium on carbon (110 mg) in acetic acid (20 ml) is hydrogenated at 0.35 bar for 23 hours. The reaction mixture is filtered and the filtrate evaporated to afford the title compound. δ_H (DMSO-d6) 1.4 (d *J* 6 6H), 3.35 (t *J* 6 1H), 3.45 (quintet *J* 6 2H), 7.1-7.3 (m 4H), 10-11 (br s 1H).

(*1S,2R,3R*)-1,3-Dimethylindan-2-ylamine

Ethyl chloroformate (0.18 ml, 1.88 mmol) is added to a cooled (0°C) solution of (*1S,2S,3R*)-1,3-dimethylindan-2-carboxylic acid (0.298 g, 1.57 mmol) and triethylamine (0.263 ml, 1.88 mmol) in acetone (3 ml) and water (0.5 ml). After 30 minutes, a solution of sodium azide (0.153 g, 2.36 mmol) in water (1 ml) is added and the reaction is stirred at 5°C for 1

hour, prior to addition of brine and ice. The mixture is extracted with ether and the combined extracts are dried (Na_2SO_4) and evaporated. The resultant acyl azide is taken into toluene (6 ml) and heated at 100°C until nitrogen evolution ceases After evaporation of solvent, the resultant isocyanate is taken into 6N HCl (2.5 ml) and heated at 100°C for 16 hours. The reaction mixture is evaporated, basified with saturated $NaHCO_3$ and extracted with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2SO_4) and evaporated to afford the title compound. *MH*+ 162.

Indan-2-ylmethylamine

Ethyl chloroformate (3.3 ml, 34 mmol) is added to a cooled (0°C) solution of indan-2-yl acetic acid (5.0 g, 28.4 mmol) and triethylamine (4.75 ml, 34 mmol) in acetone (40 ml) and water (8 ml). After 30 minutes, a solution of sodium azide (2.8 g, 42.6 mmol) in water (16 ml) is added and the reaction is stirred at 5°C for 1 hour, prior to addition of brine and ice. The mixture is extracted with ether and the combined extracts are dried (Na_2SO_4) and evaporated. The resultant acyl azide is taken into toluene (50 ml) and heated at 100°C until nitrogen evolution ceases. After evaporation of solvent, the resultant isocyanate is taken into 6N HCl (40 ml) and heated at 100°C for 16 hours. The reaction mixture is evaporated to 1/3 volume and the resultant solid collected by filtration, washed with water and ether, then dried. The resultant hydrochloride salt is suspended in ether (20 ml) and ammonia is bubbled for 10 minutes. Water is added and the organic layer is separated, dried (Na_2SO_4) and evaporated to afford the title compound $[MH + CH_3CN]^+$ 189.

Preparation of final compounds

Example 1

8-Hydroxy-5-[*R*-1-hydroxy-2-(*R*-indan-1-ylamino)ethyl]-1H-quinolin-2-one

N,O bis-(trimethylsilyl)acetamide (93 µl, 0.37 mmol) is added to a solution of *R*-1-aminoindane (96.3 µl, 0.75 mmol) in DMF (0.6 ml) and the mixture stirred at ambient temperature for 30 minutes. A solution of *R*-8-benzyloxy-5-oxiranyl-1H-quinolin-2-one (0.147 g, 0.50 mmol) in DMF (0.9 ml) is added and the mixture heated at 80°C for 36 hours. The reaction mixture is added to water and extracted with ether-EtOAc (1:1); the organic phase is evaporated and purified by flash column chromatography (EtOAc elution)

to afford 8-benzyloxy-5-[*R*-1-hydroxy-2-(*R*-indan-1-ylamino)ethyl]-1H quinolin-2-one, *MH*+ 427.

A suspension of 8-benzyloxy-5-[*R*-1-hydroxy-2-(*R*-indan-1-ylamino)ethyl]-1H quinolin-2-one (35 mg, 0.08 mmol) and 10% Pd/C (15 mg) in ethanol (11 ml) is hydrogenated at 0.35 bar for 1 hour. The reaction mixture is filtered through a Celite™ filter plug, washed with ethanol and the combined filtrate and washings are evaporated. The crude product is purified by flash column chromatography (10:1 CH_2Cl_2-MeOH elution) to afford 8-hydroxy-5-[*R*-1-hydroxy-2-(*R*-indan-1-ylamino)ethyl]-1H-quinolin-2-one, *MH*+ 337.

Example 2

8-Hydroxy-5-[*R*-1-hydroxy-2-(*S*-indan-1-ylamino)ethyl]-1H-quinolin-2-one

This is prepared using a method analogous to Example 1, *MH*+ 427 but using *S*-1-aminoindane as the starting material.

Example 3

5-[*R*-2-(*RS*-5-butylindan-1-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one

This compound is prepared using procedures analogous to those used in Example 1, using *R*-8-benzyloxy-5-oxiranyl-1H-quinolin-2-one and 5-*n*-butylindan-1-ylamine, *MH*+ 393

Example 4

8-Hydroxy-5-[*R*-1-hydroxy-2-(1*R*,2*S* -1-methylindan-2-ylamino)ethyl]-1H-quinolin-2-one and 8-hydroxy-5-[*R*-1-hydroxy-2-(1*S*,2*R*-1-methylindan-2-ylamino)ethyl]-1H-quinolin-2-one

A mixture of (+/-) *cis*-1-methylindan-2-yl amine (J. Chem. Soc. (C), 1970, 920), (0.351 g, 2.38 mmol) and *R*-8-benzyloxy-5-oxiranyl-1H-quinolin-2-one (0.350 g, 1.19 mmol) in 2-methoxyethyl ether (2 ml) is heated in a sealed tube at 190°C for 16 hours. The solvent is evaporated and the crude product purified by flash column chromatography (20:1 CH_2Cl_2-MeOH elution) to afford a 1:1 mixture of 8-benzyloxy-5-[*R*-1-hydroxy-2-(1*R*,2*S* -1-methylindan-2-ylamino)ethyl]-1H-quinolin-2-one and 8-benzyloxy-5-[*R*-1-hydroxy-2-(1*S*,2*R*-1-methylindan-2-ylamino)ethyl]-1H-quinolin-2-one, *MH*+ 441.

A suspension of 8-benzyloxy-5-[*R*-1-hydroxy-2-(1*R*,2*S* -1-methylindan-2-ylamino)ethyl]-1H-quinolin-2-one and 8-benzyloxy-5-[*R*-1-hydroxy-2-(1*S*,2*R*-1-methylindan-2-ylamino)ethyl]-1H-quinolin-2-one (0.100 g, 0.23 mmol) and 10% Pd/C (10 mg) in ethanol (8 ml) is hydrogenated at 0.35 bar for 2 hours. The reaction is filtered through a Celite™ filter plug and washed with ethanol. The combined filtrate and washings are evaporated to afford a 1:1 mixture of 8-hydroxy-5-[*R*-1-hydroxy-2-(1*R*,2*S*-1-methylindan-2-ylamino)ethyl]-1H-quinolin-2-one and 8-hydroxy-5-[*R*-1-hydroxy-2-(1*S*,2*R*-1-methylindan-2-ylamino)ethyl]-1H-quinolin-2-one, *MH*+ 351.

Example 5

8-Hydroxy-5-{*R*-1-hydroxy-2-[*R*-(1,2,3,4-tetrahydronaphthalen-1-yl)amino]-ethyl}-1H-quinolin-2-one

R-1-Amino-1,2,3,4-tetrahydronaphthalene (0.301 g, 2.0 mmol) and *R*-8-benzyloxy-5-oxiranyl-1H-quinolin-2-one (0.200 g, 0.68 mmol) are heated neat in sealed tube at 110°C for 16 hours. The crude product is purified by preparative LCMS to afford 8-benzyloxy-5-{*R*-1-hydroxy-2-[*R*-(1,2,3,4-tetrahydronaphthalen-1-yl)amino]-ethyl}-1H-quinolin-2-one, *MH*+ 441.

A suspension of 8-benzyloxy-5-{*R*-1-hydroxy-2-[*R*-(1,2,3,4-tetrahydronaphthalen-1-yl)amino]-ethyl}-1H-quinolin-2-one (0.155 g, 0.35 mmol) and 10% Pd/C (30 mg) in methanol-trifluoroacetic acid (20:1, 21 ml) is hydrogenated at 0.35 bar for 4 hours. The catalyst is filtered through a Celite™ filter plug and washed with methanol. Evaporation affords 8-hydroxy-5-{*R*-1-hydroxy-2-[*R*-(1,2,3,4-tetrahydronaphthalen-1-yl)amino]-ethyl}-1H-quinolin-2-one, *MH*+ 351.

Example 6

5-[*R*-2-(*1S,2R,3R*-1,3-Dimethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one

This compound is prepared using procedures analogous to those used in Example 4, but converting (*1S,2R,3R*)-1,3-dimethylindan-2-ylamine to 8-benzyloxy 5-[*R*-2-(*1S,2R,3R*-1,3-dimethylindan-2-ylamino)-1-hydroxyethyl]-1H-quinolin-2-one (*MH*+ 455) and deprotecting that compound to give the title compound (*MH*+ 365).

Example 7

8-Hydroxy-5-{*R*-1-hydroxy-2-[(indan-2-ylmethyl)amino]ethyl}-1H-quinolin-2-one

This compound is prepared using procedures analogous to those used in Example 1, but converting indan-2-ylmethylamine to 8-benzyloxy-5-{*R*-1-hydroxy-2-[(indan-2-ylmethyl)amino]ethyl}-1H-quinolin-2-one (*MH*+ 441) and then deprotecting that compound to give the title compound (*MH*+ 351).

Examples 8 to 20

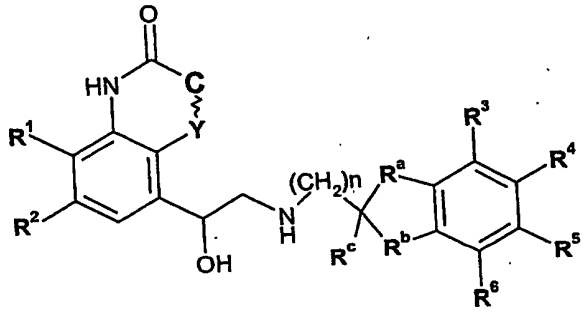
These compounds are prepared using procedures analogous to those used in Example 3, using *R*-8-benzyloxy-5-oxiranyl-1H-quinolin-2-one and the appropriate amine.

Examples 21 to 28

These compounds are prepared using procedures analogous to those used in Example 4, using *R*-8-benzyloxy-5-oxiranyl-1H-quinolin-2-one and the appropriate amine.

CLAIMS

1. A compound of formula I



I

in free or salt or solvate form, where

-C~Y- denotes $-CH_2-CH_2-$, -CH=CH- or $-CH_2-O-$;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is an integer from 0 to 4;

when n is 0, R^a is $-CR^7R^8-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-O-$, $-CH_2-O-CH_2-$, $-CH_2-S-$, $-CH_2-CH_2-S-$, $-CH_2-SO-$, $-CH_2-SO_2-$ or a bond, and R^b is $-CR^9R^{10}-$, $-CH_2-CH_2-CH_2-$, $-CH_2-O-$, $-CH_2-O-CH_2-$, $-CH_2-S-$, $-CH_2-CH_2-S-$, $-CH_2-SO-$, $-CH_2-SO_2-$ or a bond, otherwise when n is 1, 2 ,3 or 4, R^a and R^b are independently $-CR^7R^8-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, -O-, $-CH_2-O-$, $-CH_2-O-CH_2-$, -S-, -SO-, $-SO_2-$, $-CH_2-S-$, $-CH_2-CH_2-S-$, $-CH_2-SO-$, $-CH_2-SO_2-$ or a bond;

R^c is hydrogen or C_1-C_{10}-alkyl optionally substituted by a C_5-C_{15}-carbocyclic group or by C_1-C_{10}-alkoxy,

or when R^b is $-CR^7R^8-$ or $-CR^9R^{10}-$, R^c and R^b form a C_5-C_{15}-carbocyclic group;

R^3, R^4, R^5 and R^6 are independently hydrogen, halo, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, or a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, or any two of R^3, R^4, R^5 and R^6 that are attached to adjacent carbon atoms on the phenylene ring together form a phenylene ring, C_3-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkenyl or 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur;

R^7 , R^8 and R^9 are independently hydrogen, C_1-C_{10}-alkyl or C_1-C_{10}-alkoxy, either of which being optionally substituted by a C_5-C_{15}-carbocyclic group; and

R^{10} is C_1-C_{10}-alkyl or C_1-C_{10}-alkoxy, either of which being optionally substituted by a C_5-C_{15}-carbocyclic group.

2. A compound according to claim 1, where

-C~Y- is -CH=CH-;

R^1 is hydroxy and R^2 is hydrogen;

n is 0 or 1;

when n is 0, R^a is $-CR^7R^8-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-O-CH_2-$ or $-CH_2-CH_2-S-$,

and R^b is $-CR^9R^{10}-$, $-CH_2-O-$ or a bond,

otherwise when n is 1, R^a and R^b are both $-CR^7R^8-$;

R^c is hydrogen or C_1-C_{10}-alkyl optionally substituted by a C_5-C_{15}-carbocyclic group or by C_1-C_{10}-alkoxy,

or when R^b is $-CR^7R^8-$ or $-CR^9R^{10}-$, R^c and R^b form a C_5-C_{15}-carbocyclic group;

R^3, R^4, R^5 and R^6 are independently hydrogen, C_1-C_{10}-alkyl or C_1-C_{10}-alkoxy;

R^7 , R^8 and R^9 are independently hydrogen, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur; and

R^{10} is C_1-C_{10}-alkyl or C_1-C_{10}-alkoxy.

3. A compound according to claim 2, where

-C~Y- is -CH=CH-;

R^1 is hydroxy and R^2 is hydrogen;

n is 0 or 1;

when n is 0, R^a is $-CR^7R^8-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-O-CH_2-$ or $-CH_2-CH_2-S-$,

and R^b is $-CR^9R^{10}-$, $-CH_2-O-$ or a bond,

otherwise when n is 1, R^a and R^b are both $-CR^7R^8-$;

R^c is hydrogen or C_1-C_4-alkyl optionally substituted by a C_5-C_{10}-carbocyclic group or by C_1-C_4-alkoxy,

or when R^b is $-CR^7R^8-$ or $-CR^9R^{10}-$, R^c and R^b form a C_5-C_{10}-carbocyclic group;

R^3, R^4, R^5 and R^6 are independently hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy;

R^7 , R^8 and R^9 are independently hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy or a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur; and

R^{10} is C_1-C_4-alkyl or C_1-C_4-alkoxy.

4. A compound according to claim 1 substantially as herein described with reference to any one of the Examples.

5. A compound according to any one of the preceding claims for use as a pharmaceutical.

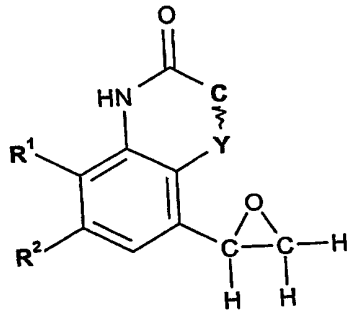
6. A pharmaceutical composition comprising a compound according to any one of the preceding claims, optionally together with a pharmaceutically acceptable carrier.

7. Use of a compound according to any one of claims 1 to 4 for the preparation of a medicament for the treatment of a condition which is prevented or alleviated by activation of the β_2-adrenoreceptor.

8. Use of a compound according to any one of claims 1 to 4 for the preparation of a medicament for the treatment of an obstructive or inflammatory airways disease.

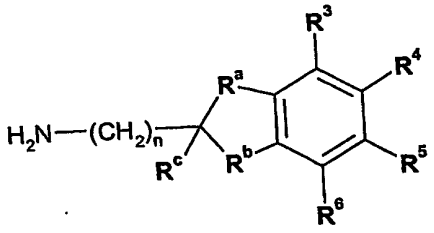
9. A process for the preparation of a compound of formula I in free or salt or solvate form comprising:

(i) (A) reacting a compound of formula II



II

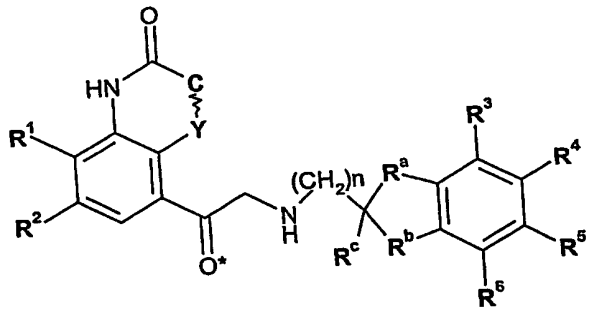
or a protected form thereof wherein -C-Y-, R^1 and R^2 are as hereinbefore defined, with a compound of formula III



III

or a protected form thereof wherein R^a, R^b, R^c, R^3, R^4, R^5, R^6 and n are as hereinbefore defined;

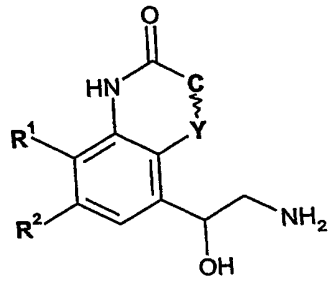
(B) reducing a compound of formula IV



IV

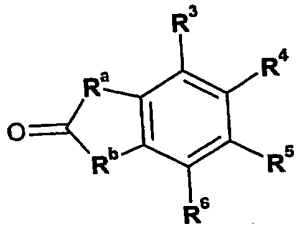
or a protected form thereof wherein -C~Y-, R^a, R^b, R^c, R^1, R^2, R^3, R^4, R^5, R^6 and n are as hereinbefore defined, to convert the indicated keto group into -CH(OH); or

(C) for the preparation of compounds of formula I where R^c is hydrogen and n is 0 reacting a compound of formula V



V

or a protected form thereof wherein -C~Y-, R^1 and R^2 are as hereinbefore defined, with a compound of formula VI

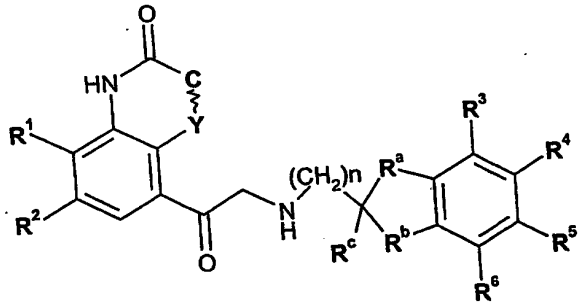


VI

or a protected form thereof wherein R^a, R^b, R^3, R^4, R^5 and R^6 are as hereinbefore defined; and

(ii) recovering the resultant compound of formula I in free or salt or solvate form.

10. A compound of formula IV



IV

in free or salt or solvate form, where

-C~Y- denotes $-CH_2-CH_2-$, -CH=CH- or $-CH_2-O-$;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is an integer from 0 to 4;

when n is 0, R^a is $-CR^7R^8-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-O-$, $-CH_2-O-CH_2-$, $-CH_2-S-$, $-CH_2-CH_2-S-$, $-CH_2-SO-$, $-CH_2-SO_2-$ or a bond, and R^b is $-CR^9R^{10}-$, $-CH_2-CH_2-CH_2-$, $-CH_2-O-$, $-CH_2-O-CH_2-$, $-CH_2-S-$, $-CH_2-CH_2-S-$, $-CH_2-SO-$, $-CH_2-SO_2-$ or a bond, otherwise when n is 1, 2 ,3 or 4, R^a and R^b are independently $-CR^7R^8-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, -O-, $-CH_2-O-$, $-CH_2-O-CH_2-$, -S-, -SO-, $-SO_2-$, $-CH_2-S-$, $-CH_2-CH_2-S-$, $-CH_2-SO-$, $-CH_2-SO_2-$ or a bond;

R^c is hydrogen or C_1-C_{10}-alkyl optionally substituted by a C_5-C_{15}-carbocyclic group or by C_1-C_{10}-alkoxy,

or when R^b is $-CR^7R^8-$ or $-CR^9R^{10}-$, R^c and R^b form a C_5-C_{15}-carbocyclic group;

R^3, R^4, R^5 and R^6 are independently hydrogen, halo, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, or a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, or any two of R^3, R^4, R^5 and R^6 that are attached to adjacent carbon atoms on the phenylene ring together form a phenylene ring, C_3-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkenyl or 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur;

R^7 , R^8 and R^9 are independently hydrogen, C_1-C_{10}-alkyl or C_1-C_{10}-alkoxy, either of which being optionally substituted by a C_5-C_{15}-carbocyclic group; and

R^{10} is C_1-C_{10}-alkyl or C_1-C_{10}-alkoxy, either of which being optionally substituted by a C_5-C_{15}-carbocyclic group.